



1623  
PATENT  
Confirmation No.: 7688  
JW

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:

Jakob Vinten-Johnasen

Examiner:

Unassigned

Serial No.:

10/562,757

Group Art Unit:

Unassigned

Filed:

02 July 2004

Docket No.:

14507-53463

Title:

**COMPOSITIONS AND METHODS FOR USE OF A PROTEASE INHIBITOR AND ADENOSINE FOR PREVENTING ORGAN ISCHEMIA AND REPERFUSION INJURY**

**CERTIFICATE UNDER 37 CFR 1.8:**

I hereby certify that this correspondence is being deposited on September 19, 2006 with the United States Postal Service as first class mail, with sufficient postage, in an envelope addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

By: 

Name: Tim Tingkang Xia

TRANSMITTAL

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

We are transmitting herewith the attached:

- Transmittal Sheet containing Certificate of Mailing (1 page)
- Supplemental Information Disclosure Statement (37 C.F.R. § 1.97(b)) (2 pages)
- Form PTO-1449 Listing Sixty-six (66) References (5 pages)
- Return postcard

MORRIS, MANNING & MARTIN, LLP  
1600 Atlanta Financial Center  
3343 Peachtree Road NE  
Atlanta, Georgia 30326  
404.495.3678  
Customer No. 24728

By:   
Name: Tim Tingkang Xia, Esq.  
Reg. No.: 45,242  
TTX



10/562,757

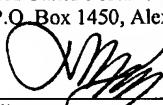
PATENT  
Confirmation No.: 7688IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Jakob Vinten-Johnasen	Examiner:	Unassigned
Serial No.:	10/562,757	Group Art Unit:	Unassigned
Filed:	02 July 2004	Docket No.:	14507-53463
Title:	<b>COMPOSITIONS AND METHODS FOR USE OF A PROTEASE INHIBITOR AND ADENOSINE FOR PREVENTING ORGAN ISCHEMIA AND REPERFUSION INJURY</b>		

**CERTIFICATE UNDER 37 CFR 1.8:**

I hereby certify that this correspondence is being deposited on September 19, 2006 with the United States Postal Service as first class mail, with sufficient postage, in an envelope addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

By: \_\_\_\_\_  
Name: Tim Tingkang Xia



Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

**Customer No. 24728****SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT (37 C.F.R. § 1.97(b))**

Dear Sir:

With regard to the above-identified application, the items of information listed on the enclosed Form 1449 are brought to the attention of the Examiner.

In accordance with 37 C.F.R. §1.98(a)(2), a copy of each non-U.S. patent document or other information listed on the enclosed Form 1449 is provided herewith, if applicable.

No representation is made that a reference is "prior art" within the meaning of 35 U.S.C. §§ 102 and 103 and Applicants reserve the right, pursuant to 37 C.F.R. § 1.131 or otherwise, to establish that the reference(s) are not "prior art." Moreover, Applicants do not represent that a reference has been thoroughly reviewed or that any relevance of any portion of a reference is intended.

Consideration of the items listed is respectfully requested. Pursuant to the provisions of M.P.E.P. 609, it is requested that the Examiner return a copy of the attached Form 1449, marked as being considered and initialed by the Examiner, to the undersigned with the next official communication.

Respectfully submitted,

MORRIS, MANNING & MARTIN, LLP



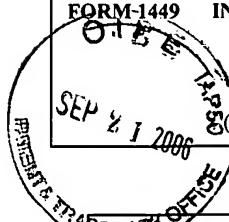
---

Tim Tingkang Xia, Esq.  
Reg. No. 45,242  
Attorney for Applicant on the Record  
TTX

September 19, 2006

MORRIS, MANNING & MARTIN, LLP  
1600 Atlanta Financial Center  
3343 Peachtree Road, N.E.  
Atlanta, Georgia 30326-1044  
Phone: 404-233-7000  
Direct: 404-495-3678  
**Customer No. 24728**

<b>FORM-1449</b> <b>INFORMATION DISCLOSURE STATEMENT</b> <b>IN AN APPLICATION</b> <small>(Use several sheets if necessary)</small>	Docket Number:	14507-53463
	Serial Number:	10/562,757
	Applicant:	Jakob Vinent-Johnasen



**-U.S. PATENT DOCUMENTS**

## **FOREIGN PATENT DOCUMENTS**

**OTHER DOCUMENTS** (Including Author, Title, Date, Pertinent Pages, Etc.)

	1	Deguchi H, Takeya H, Urano H, Gabazza EC, Zhou H, Suzuki K. Adenosine regulates tissue factor expression on endothelial cells. <i>Thromb Res</i> 1998; 91 (2): 57-64.
	2	Gabazza EC, Hayashi T, Ido M, Adachi Y, Suzuki K. Adenosine inhibits thrombin-induced expression of tissue factor on endothelial cells by a nitric oxide-mediated mechanism. <i>Clin Sci</i> 2002; 102: 167-175.
	3	Kaur J, Woodman RC, Ostrovsky L, Kubes P. Selective recruitment of neutrophils and lymphocytes by thrombin: a role for <i>Am J Physiol (Heart Circ Physiol)</i> 2001; 281:H784-H795.
	4	Cirino G, Cicala C, Bucci MR, Sorrentino L, Maraganore JM, Stone SR. Thrombin functions as an inflammatory mediator through activation of its receptor. <i>The Journal of Experimental Medicine</i> 1996; 183 (3): 821-827.
	5	Jordan JE, Zhao Z-Q, Sato H, Taft S, and Vinten-Johansen J. Adenosine A2 receptor activation attenuates reperfusion injury by inhibiting neutrophil accumulation, superoxide generation and coronary endothelial adherence. <i>J Phamacol Exp Ther</i> 1997; 280(1): 301-309.
	6	Zhao Z-Q, Sato H, Vinten-Johansen J. Adenosine a2-receptor activation inhibits neutrophil-mediated injury to coronary endothelium by attenuating superoxide anion generation and adherence. <i>Circulation (Suppl)</i> 90 (No. 4, Part 2), I- 372.1994.
	7	Zhao Z-Q, Sato H, Williams MW, Fernandez AZ, Vinten-Johansen J. Adenosine A2-receptor activation inhibits neutrophil-mediated injury to coronary endothelium. <i>Am J Physiol</i> 1996; 271 (4 Pt. 2):H1456-H1464.

**EXAMINER** \_\_\_\_\_ **DATE CONSIDERED** \_\_\_\_\_

**EXAMINER:** Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form for next communication to the Applicant.

<b>FORM 1449 INFORMATION DISCLOSURE STATEMENT</b>		Docket Number: 14507-53463	Serial Number: 10/562,757
<b>IN AN APPLICATION</b>  (Use several sheets if necessary)		Applicant: Jakob Vinten-Johnsen	Date Mailed: September 19, 2006
		Filing Date: 02 July 2004	Group Art Unit: Unassigned

8	Zhao Z-Q, Nakamura M, Wang N-P, Wilcox JN, Shearer ST, Guyton RA Vinten-Johansen J. <i>Administration of adenosine during reperfusion reduces injury of vascular endothelium and death of myocytes.</i> Coron Artery Dis. 1999; 10 (8): 617- 28.
9	Zhao Z-Q, Todd JC, Sato H, <i>Adenosine inhibition of neutrophil damage during reperfusion does not involve K (ATP)-channel activation.</i> Am J Physiol 1997; 273(4 Pt.2):H1677-H1687.
10	Zhao Z-Q, Nakamura M, Wang N-P, Wilcox JN, Shearer ST, Katzmark S et al. <i>Adenosine during early reperfusion reduces neutrophil-mediated necrosis, apoptosis and vascular dysfunction.</i> FASEB Journal 13[4] A518. 1999.
11	Asimakopoulos G, Thompson R, Nourshargh S, Lidington EA, Mason JC, Ratnatunga CP et al. <i>An anti-inflammatory property of aprotinin detected at the level of leukocyte extravasation.</i> Journal Thoracic Cardiovascular Surg 2000; 120: 361-369.
12	Jennings RB, Reimer KA. <i>Acute myocardial ischemia: effects of reperfusion with arterial blood.</i> Artif Cells Blood Substit Immobil Biotechnol 1994; 22:253-278.
13	Reimer KA, Jennings RB. The "wavefront phenomenon" of myocardial ischemic cell death. Transmural progression of necrosis within the framework of ischemic bed size (myocardium at risk) and collateral flow. Lab Invest 1979; 40: 633-644.
14	Zhao Z-Q, Nakamura M, Wang N-P, Wilcox JN, Katzmark S, Guyton RA et al. <i>Infarct extension and dynamic coronary endothelial dysfunction in the late reperfusion phase.</i> Circulation 1998; 98 (17):I-796.:.
15	Poullis M, Manning R, Laffan M, Haskard DO, Taylor KM, Landis RC. <i>The antithrombotic effect of aprotinin: actions mediated via the protease- activated receptor 1.</i> The Journal of Thoracic and Cardiovascular Surgery 2000; 120 (2): 370-378.
16	Kubes P. <i>Polymorphonuclear leukocyte-endothelium interactions: a role for pro-inflammatory and anti-inflammatory molecules.</i> [Review]. Can J Physiol Pharmacol 1993; 71: 88-97.
17	Deisher TA, Garcia I, Harlan JM. <i>Cytokine-induced adhesion molecule expression on human umbilical vein endothelial cells is not regulated by cyclic adenosine monophosphate accumulation.</i> Life Sci 1993; 53: 365-370.
18	Erlich JH, Boyle EM, Labriola J, Kovacich JC, Santucci RA, Fearn C et al. <i>Inhibition of the tissue factor-thrombin pathway limits infarct size after myocardial ischemia-reperfusion injury by reducing inflammation.</i> Am J Pathol 2000; 157(6):1849-1862.
19	Davenport KL, Gauthier TW, Albertine KH, Lefer AM. <i>Role of selectin in microvascular leukocyte-endothelial interaction in ischemia- reperfusion.</i> Am J Physiol 1994; 267: H622-30.
20	Foreman KE, Vaporciyan AA, Bonish BK, Jones ML, Johnson KJ, Glovsky MM et al. <i>C5a-induced expression of P-selectin in endothelial cells.</i> J Clin Invest 1994; 94 (3): 1147-1155.
21	Lefer AM. <i>Role of selectins in myocardial ischemia-reperfusion injury.</i> [Review]. Ann Thorac Surg 1995; 60: 773-777.
22	Sheridan FM, Cole PG, Ramage D. <i>Leukocyte adhesion to the coronary microvasculature during ischemia and reperfusion in an in vivo canine model.</i> Circulation 1996; 93:1784-1787.
23	Lefer AM, Tsao PS, Lefer DJ, Ma X-L. <i>Role of endothelial dysfunction in the pathogenesis of reperfusion injury after myocardial ischemia.</i> FASEB J 1991; 5: 2029-2034.
24	Jordan JE, Zhao Z-Q, Vinten-Johansen J. <i>The role of neutrophils in myocardial ischemia-reperfusion injury.</i> Cardiovas Res 1999; 43: 860-878.
25	Lefer AM, Ma X-L, Weyrich A, Lefer DJ. <i>Endothelial dysfunction and neutrophil adherence as critical events in the development of reperfusion injury.</i> Agents Actions Suppl 1993; 41: 127-135.
26	Lefer DJ, Nakanishi K, Vinten-Johansen J, Ma X-L, Lefer AM. <i>Cardiac venous endothelial dysfunction after myocardial ischemia and reperfusion in dogs.</i> Am J Physiol 1992; 263:H850-H856.

EXAMINER	DATE CONSIDERED
EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form for next communication to the Applicant.	

<b>FORM 1449 INFORMATION DISCLOSURE STATEMENT</b>		Docket Number: 14507-53463	Serial Number: 10/562,757
IN AN APPLICATION  (Use several sheets if necessary)		Applicant: Jakob Vinten-Johnasen	Date Mailed: September 19, 2006
		Filing Date: 02 July 2004	Group Art Unit: Unassigned

	27	Boyle EM, Pohlman TH, Cornejo CJ, Verrier ED. <i>Endothelial cell injury in cardiovascular surgery: Ischemia-reperfusion</i> . Ann Thorac Surg 1996; 62:1868-1875.
	28	Tsao PS, Aoki N, Lefer DJ, Johnson G, III, Lefer AM. <i>Time course of endothelial dysfunction and myocardial injury during myocardial ischemia and reperfusion in the cat</i> . Circulation 1990; 82: 1402-1412.
	29	Geng J-G, Bevilacqua MP, Moore KL, McIntyre TM, Prescott SM, Kim JM et al. <i>Rapid neutrophil adhesion to activated endothelium mediated by GMP- 140</i> . Nat 1990; 343: 757-760.
	30	Jerome SN, Dore M, Paulson JC, Smith CW, Korthuis RJ. <i>P-selectin and ICAM-1 dependent adherence reactions: role in the genesis of postischemic no-reflow</i> . Am J Physiol 1994; 266:H1316-21.
	31	Kubes P, Jutila M, Payne D. <i>Therapeutic potential of inhibiting leukocyte rolling in ischemia/reperfusion</i> J Clin Invest 1995; 95: 2510-2519.
	32	Golino P, Ragni M, Cirillo P, A, Ravera A, Buono C, Guarino A, Piro Lambiase C, Botticella F, Ezban M, Condorelli M, Chiariello M. <i>Recombinant human, active site-blocked factor VIIa reduces infarct size and no-reflow phenomenon in rabbits</i> . Am J Physiol Heart Circ Physiol. 2000; 278(5):H1507-16.
	33	Zhao Z-Q, Nakamura M, Wang N-P, Velez DA, Hewan-Lowe KO, Guyton RA et al. <i>Dynamic progression of contractile and endothelial dysfunction and infarct extension in the late phase of reperfusion</i> . J Surg Res 2000; 94: 1-12.
	34	Zhao Z-Q, Nakamura M, Wang N-P, Wilcox JN, Shearer S, Ronson RS et al. <i>Reperfusion induces myocardial apoptotic cell death</i> . Cardiovasc Res 2000; 45: 651-660.
	35	Cronstein BN, Kramer SB, Weissmann G, Hirschhorn R. <i>Adenosine: A physiological modulator of superoxide anion generation by human neutrophils</i> . J Exp Med 1983; 158:1160-1177.
	36	Cronstein BN, Rosenstein ED, Kramer SB, Weissmann G, Hirschhorn R. <i>Adenosine: a physiologic modulator of superoxide anion generation by human neutrophils. Adenosine acts via an receptor on human neutrophils</i> . J Immunol 1985 ; 135 (12): 1366-1371.
	37	Jordan JE, Thourani VH, Auchampach JA, Robinson JA, Wang N-P, Vinten-Johansen J. <i>A3 adenosine receptor activation attenuates neutrophil function and neutrophil-mediated reperfusion injury</i> . Am J Physiol 1999; 277:H1895-H1905:
	38	Olafsson B, Forman MB, Puett DW, Pou A, Cates CU, Friesinger GC et al. <i>Reduction of reperfusion injury in the canine preparation by intracoronary adenosine: importance of the endothelium and the no-reflow phenomenon</i> . Circulation 1987; 76 (5): 1135-1145.
	39	Toombs CF, McGee DS, Johnston WE, Vinten-Hohansen J. <i>Myocardial protective effects of adenosine. Infarct size reduction with pretreatment and continued receptor stimulation during ischemia</i> . Circulation 1992; 86: 986-994.
	40	Budde JM, Velez DA, Zhao Z-Q, Clark KL, Morris CD, Muraki S et al. <i>Comparative study of AMP579 and adenosine in inhibition of neutrophil-mediated vascular and myocardial injury during 24 hours of reperfusion</i> . Cardiovas Res 2000; 47: 294-305.
	41	Nakamura M, Zhao Z-Q, Clark KL, Guyton RA, Vinten-Johansen J. <i>AMP579, a new adenosine analog, inhibits neutrophil O2-generation, degranulation, adherence, and neutrophil-induced injury to coronary vascular endothelium by A2A receptor mechanism</i> . Circulation 100[18], I-832.1999.
	42	Nakamura M, Zhao Z-Q, Clark KL, Velez DV, Guyton RA, Vinten- Johansen J. <i>A novel adenosine analog, AMP579, inhibits neutrophil activation, adherence and neutrophil-mediated injury to coronary vascular endothelium</i> . Eur J Pharmacol. 2000; 397(1): 197-205.
	43	Zhao Z-Q, Clark KL, Wang N-P, Velez DA, Guyton RA, Vinten- Johansen J. <i>Comparison of AMP579 and adenosine in inhibition of cell-cell interaction between human neutrophil and vascular endothelial cell</i> . Drug Devel Res 2000; 49: 266-272.
	44	Babbitt DG, Virmani R, Forman MB. <i>Intracoronary adenosine administered after reperfusion limits vascular injury after prolonged ischemia in the canine model</i> . Circulation 1989; 80: 1388-1399.

EXAMINER	DATE CONSIDERED
EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form for next communication to the Applicant.	

<b>FORM 1449 INFORMATION DISCLOSURE STATEMENT</b> <b>IN AN APPLICATION</b> <small>(Use several sheets if necessary)</small>		Docket Number: 14507-53463	Serial Number: 10/562,757
		Applicant: Jakob Vinten-Johansen	Date Mailed: September 19, 2006
		Filing Date: 02 July 2004	Group Art Unit: Unassigned

	45	Babbitt DG, Virmani R, Vildibill HD, Jr., Norton ED, Forman MB. <i>Intracoronary adenosine administration during reperfusion following 3 hours of ischemia: effects on infarct size, ventricular function, and regional myocardial blood flow.</i> Am Heart J 1990; 120: 808-818.
	46	Schlack W, Schäfer M, Uebing A, Schäfer S, Borchard U, Tamer V. <i>Adenosine A2-receptor activation at reperfusion reduces infarct size and improves myocardial wall function in dog heart.</i> J Cardiovasc Pharmacol 1993; 22: 89-96.
	47	Todd JC, Zhao Z-Q, Williams MW, Sato H, Van Wylen DGL, Vinten- Johansen J. <i>Intravascular adenosine at reperfusion reduces infarct size and neutrophil adherence.</i> Ann Thorac Surg 1996; 62: 1364-1372.
	48	Hearse DJ, Stewart DA, Braimbridge MV. <i>Cellular protection during myocardial ischemia. The development and characterization of a procedure for the induction of reversible ischemic arrest.</i> Circulation 1976; 54: 193-202.
	49	Hudspeth DA, Nakanishi K, Vinten-Johansen J, Zhao Z-Q, McGee DS, Williams MW et al. <i>Adenosine in blood cardioplegia prevents postischemic dysfunction in ischemically injured hearts.</i> Ann Thorac Surg 1994; 58: 1637-1644.
	50	Thourani VH, Ronson RS, Van Wylen DGL, Shearer ST, Katzmark SL, Zhao Z-Q et al. <i>Adenosine-supplemented blood cardioplegia attenuates postischemic dysfunction after severe regional ischemia.</i> Circulation 1999; 100 [suppl]:11-376-II-383.
	51	Guyton RA, Thourani VH, Puskas JD, Shanewise JS, Steele MA, Palmer-Steele CL et al. <i>Perfusion-assisted direct coronary artery bypass: selective graft perfusion in off-pump cases.</i> Ann Thorac Surg 2000; 69: 171-175.
	52	Muraki S, Morris CD, Budde JM, Velez DA, Zhao Z-Q, Guyton RA et al. <i>Experimental off-pump coronary artery revascularization with adenosine enhanced reperfusion.</i> J Thorac Cardiovasc Surg 2001; 121 (3): 570-579.
	53	McCarthy RJ, Tuman KJ, O'Connor C, Ivankovich AD. <i>Aprotinin pretreatment diminishes postischemic myocardial contractile dysfunction in dogs.</i> Anesth Analg 1999; 89(5):1096.
	54	Buerke Pruefer D, Dahin M, Oelert H, Meyer J. <i>Serine protease inhibitor (Aprotinin) attenuates myocardial necrosis and apoptosis following ischaemia and long-term reperfusion in rats.</i> European Heart Journal 20 [P996], 163. 1999.
	55	Sunamori M, Sultan I, Suzuki A. <i>Effect of aprotinin to improve myocardial viability in myocardial preservation followed by reperfusion.</i> Ann Thorac Surg 1991; 52:971-978.
	56	Gurevitch J, Barak J, Hochhauser E, Paz Y, Yakirevich V. <i>Aprotinin improves myocardial recovery after ischemia and reperfusion. Effects of the drug on isolated rat hearts.</i> J Thorac Cardiovasc Surg 1994; 108:109-118.
	57	Lord RA, Roath OS, Thompson JF, Chant ADB, Francis JL. <i>Effect of aprotinin on neutrophil function after major vascular surgery.</i> Br J Surg 1992; 79: 517- 521.
	58	Hallett Shandall A, Young HL. <i>Mechanism of protection against "reperfusion injury"by aprotinin. Roles of polymorphonuclear leucocytes and oxygen radicals.</i> 1995; 34 (10): 1757-1761.
	59	Buerke M, Weyrich AS, Lefer AM. <i>Isolated cardiac myocytes are sensitized by hypoxia-reoxygenation to neutrophil-released mediators.</i> Am J Physiol 1994; 266:H128-H136.
	60	Asimakopoulos G, Lidington EA, Mason JC, Haskard DO, Taylor KM, Landis RC. <i>Effect of aprotinin on endothelial cell activation.</i> Journal Thoracic Cardiovascular Surg 2001; 122(I):123-128.
	61	Asimakopoulos G, Kohn A, Stefanou DC, Haskard DO, Landis RC, Taylor KM. <i>Leukocyte integrin expression in patients undergoing cardiopulmonary bypass.</i> The Society of Thoracic Surgeons 2000; 69(4):1192-1197.
	62	Asimakopoulos G, Taylor KM, Haskard DO, Landis RC. <i>Inhibition of neutrophil L-selectin shedding: a potential anti-inflammatory effect of aprotinin.</i> Perfusion 2000; 15(6):495-499.
	63	Himmelfarb J, Holbrook D, McMonagle E. <i>Effects of Aprotinin on complement and granulocyte activation during ex vivo hemodialysis.</i> Am J of Kidney Diseases 1994; 24 (6): 901-906.

EXAMINER	DATE CONSIDERED
EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form for next communication to the Applicant.	

<b>FORM 1449 INFORMATION DISCLOSURE STATEMENT</b>		Docket Number: 14507-53463	Serial Number: 10/562,757
IN AN APPLICATION  (Use several sheets if necessary)		Applicant: Jakob Vinten-Johnsen	Date Mailed: September 19, 2006
		Filing Date: 02 July 2004	Group Art Unit: Unassigned

64	Hill GE, Alonso A, Spurzem JR, Stammers AH, Robbins RA. <i>Aprotinin and methylprednisolone equally blunt cardiopulmonary bypass-induced inflammation in humans.</i> J Thorac Cardiovasc Surg 1995; 110:1658-1662;
65	Englberger L, Kipfer B, Berdat PA, Nydegger Carrel TP. <i>Aprotinin in coronary operation with bypass: does "low-dose" aprotinin inhibit the inflammatory response?</i> Ann Thorac Surg 2002; 73(6):1897- 1904.
66	Askenazi J, Hillis LD, Diaz PE, Davis MA, Braunwald E, Maroko PR. <i>The effects of hyaluronidase on coronary blood flow following coronary artery occlusion in the dog.</i> AM J Cardiol 1977; 40 (6): 566-571
67	
68	

**Customer No. 24728**

EXAMINER	DATE CONSIDERED
----------	-----------------

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form for next communication to the Applicant.